

REMARKS

Favorable consideration of the subject application, in light of the following remarks, are respectfully requested.

The Examiner has required Applicants to make two separate elections based upon the alleged lack of unity of invention in the present national stage application.

In response, Applicants hereby elect, with traverse:

- **Group (a)**, claims 1-14, characterized by the Examiner as being drawn to an isolated nucleic acid molecule comprising SEQ ID NO: 1, the complement of said sequence, sequences having at least 80% identity to said sequence and nucleotide sequences which hybridize to said sequence; and further wherein said nucleic acid molecules are used as a marker for determining the differentiation of human stem cells; and
- the single nucleic acid molecule of **Group (1)**, SEQ ID NO: 84.

Applicants respectfully request that the Examiner reconsider the particular invention groupings since Groups (a)-(f), and similarly Groups 1-4, are linked so as to form a single general inventive concept.

Group (a), which Applicants have elected, comprises SEQ ID NO:1, which as indicated in Table 1 of the specification is identified as miR-302b*. SEQ ID NOS: 2-6 are identified as miR-302b, miR-302c*, miR-302c, miR-302a*, and miR-302d, respectively. See Specification at 6-7, Table 1. SEQ ID NO: 84, the single nucleic acid molecule that Applicants have elected, is the precursor for miR-302b* and miR-302b. SEQ ID NOS: 85-87 are the precursors for miR-302c* and miR-302c; miR-302a* and miR-302a; and miR-302d, respectively. See Paper Copy of Sequence Listing.

Each of miR-302a, miR-302b, miR-302c, and miR-302d are isolated from human embryonic stem cell and clustered in human chromosome IV. The cluster of miR-302a, miR-302b, miR-302c, and miR-302d can be used for determination of stem cell type, for distinguishing between human embryonic stem cells and mouse embryonic stem cells, and for selecting human embryonic stem cells or human embryonic carcinoma stem cells. See Specification at 16 (line 7) - 17 (line 9)..

The clustering of miR-302a, miR-302b, miR-302c and miR-302d is also disclosed in the referenced miRNA database (<http://microma.sanger.ac.uk>). The database discloses 21 miRNA as a mir-302 gene family (see enclosed Reference 1 (http://microrna.sanger.ac.uk/cgi-bin/sequences/mirna_summary.pl?fam=MIPF000071)). Among the mir-302 gene family, hsa-mir302a, hsa-mir302b, hsa-mir302c and hsa-mir302d correspond miR-302a, miR-302b, miR-302c, miR-302d, respectively (see enclosed References 2 to 5, the stem loop structures of References 2 to 5 are the same as the structure of Fig 1 of the present invention, respectively.)

Moreover, nucleotides of SEQ ID NO:1 to 6 have high sequence homology (78%) to each other. (In Reference 6, panel A is the result of analyzing the sequence homology of precursor of siRNA of the present invention; and panel B is the result of analyzing the sequence homology of siRNA of the present invention).

Therefore, nucleotides of SEQ ID NO:1-6 are members of the miR-302 gene family (and SEQ ID NO: 84-87 as precursors). As such Groups (a)-(f) and Groups 1-4 are linked so as to form a general inventive concept and thus possess unity of invention. In view of the foregoing, the examiner is respectfully requested to

combine Groups (b)-(f) with already elected Group (a), and to combine Group 2-4 with already elected Group 1.

Applicants response is made without prejudice or disclaimer to any non-elected subject matter, and Applicants reserve the right to file one or more continuation and/or divisional applications directed to any non-elected subject matter.

In view of the foregoing, further favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

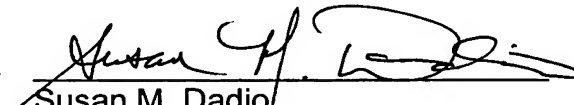
In the event that there are any questions related to this response, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at the below-listed telephone number concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: August 18, 2008

By:


Susan M. Dadio
Registration No. 40,373






















P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620



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miRNA gene family: mir-302 (21 sequences)




ID	Accession	Chromosome	Start	End	Strand	Fetch
gga-mir-302a	MI00012141	4	58651879	58651945	+	
gga-mir-302b	MI0003700	4	58651314	58651385	+	
gga-mir-302c	MI0003701	4	58651576	58651640	+	
gga-mir-302d	MI0003702	4	58652214	58652282	+	
hsa-mir-302a	MI0000738	4	113788788	113788856	-	
hsa-mir-302b	MI0000772	4	113789090	113789162	-	
hsa-mir-302c	MI0000773	4	113788968	113789035	-	
hsa-mir-302d	MI0000774	4	113788609	113788676	-	
mdo-mir-302a	MI0005373	5	66074649	66074718	-	
mdo-mir-302b	MI0005371	5	66075008	66075078	-	
mdo-mir-302c	MI0005372	5	66074864	66074922	-	
mdo-mir-302d	MI0005374	5	66074486	66074556	-	
mmi-mir-302a	MI0007687	5	105472356	105472424	-	
mmi-mir-302b	MI0007688	5	105472668	105472743	-	
mmi-mir-302c	MI0007689	5	105472533	105472600	-	
mmi-mir-302d	MI0007690	5	105472190	105472257	-	
mmu-mir-302a	MI0000402	3	127248414	127248482	+	
mmu-mir-302b	MI0003716	3	127248146	127248219	+	
mmu-mir-302c	MI0003717	3	127248281	127248348	+	
mmu-mir-302d	MI0003718	3	127248542	127248607	+	
xir-mir-302	MI0004878	scaffold_89	1068787	1068855	-	

Get selected sequences:

Select sequences and output type, then click "Fetch Sequences":

Stem-loop sequence 

Unaligned fasta format 

miRNA gene family: mir-302 (21 sequences)

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Stem-loop sequence MI0000738

Accession MI0000738**ID** hsa-mir-302a**Symbol** HGENC.MIRN302A**Description** Homo sapiens miR-302a stem-loop**Stem-loop**[Get sequence](#)**Comments**

miR-302 was first cloned from mouse embryonic stem cells (MI0000402) [1]. Human miR-302 was predicted based on homology with mouse [3], and later confirmed by cloning in human embryonic stem cells. miR-302a is located in a cluster with the related miRNAs miR-302b (MI0000772), miR-302c (MI0000773), miR-302d (MI0000774) and miR-367 (MI0000775) on human chromosome 4.

Coordinates
(NCBI36)

4: 113788788

113788856 [1]

Overlapping transcripts

antisense

OTTHUMT00000256417

AC106864.1-001

intron 8

ENST00000344442

LARP7 intron 8

ENST00000324052

LARP7 HUMAN

intron 8

ENST00000308878

04G013-2 intron 8

Genome
context[View flanking features](#)

< 10kb from hsa-mir

Clustered miRNAs	<i>302a</i>	
	hsa-miR-302b	4: 113789090-113789162
	hsa-miR-302c	4: 113788968-113789035
	hsa-miR-302a	4: 113788788-113788856
	hsa-miR-302d	4: 113788609-113788676
	hsa-miR-367	4: 113788479-113788546
Database links	HGNC: 31623, MIRN302A	
Gene family	MIPF0000071, mi-302	

Mature sequence MIMAT0000684

Accession	MIMAT0000684
ID	hsa-miR-302a
Sequence	<p>44 - 66</p> <p>Get sequence</p>
Evidence	experimental, cloned [2,4], Northern [2]
Predicted targets	<p>MIRANDA: hsa-miR-302a</p> <p>TARGETSCAN: hsa-miR-302a</p> <p>PICTAR-VERT: hsa-miR-302a</p> <p>PICTAR-VERT: hsa-miR-302a</p>

Minor miR* sequence MIMAT0000683

Accession	MIMAT0000683
ID	hsa-miR-302a*
Sequence	<p>6 - 28</p> <p>Get sequence</p>
Evidence	experimental, cloned [2,4], Northern [2]

**Predicted
targets**

MIRANDA: hsa-miR-302a
TARGETSCAN: hsa-miR-302a

References

- 1 'Embryonic stem cell-specific MicroRNAs'
Houbaviy HB, Murray MF, Sharp PA
Dev Cell. 5:351-358(2003).
- 2 'Human embryonic stem cells express a unique set of microRNAs'
Sun MR, Lee Y, Kim JY, Kim SK, Moon SH, Lee JY, Cha KY, Chung HM,
Yoon HS, Moon SY, Kim VN, Kim KS
Dev Biol. 270:488-498(2004)
- 3 'New human and mouse microRNA genes found by homology search'
Weber MJ
FEBS J. 272:59-73(2005)
- 4 'A mammalian microRNA expression atlas based on small RNA library
sequencing'
Landgraf P, Rust M, Sheridan R, Sewer A, Iovino N, Aravin A, Pfeffer S,
Rice A, Knapphorst AO, Landthaler M, Lin C, Sockanathan ND, Hermida L, Földes
V, Charette SF, Foa R, Schilwaka J, Euchs U, Novoselec A, Müller RU,
Schermer B, Bissels U, Jaman J, Phan Q, Chien M
Cell. 129:1401-1414(2007)

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Stem-loop sequence MI0000772

Accession MI0000772**ID** hsa-mir-302b**Symbol** HGNC:MIRN302B**Description** Homo sapiens miR-302b stem-loop**Stem-loop**[Get sequence](#)**Comments**

Human miR-302a (MI0000738), miR-302b (MI0000772), miR-302c (MI0000773), miR-302d (MI0000774) and miR-367 (MI0000775) are clustered on chromosome 4. The mature sequence shown here represents the most commonly cloned form from large-scale cloning studies [2].

Coordinates
(NCBI36)

4: 113789090-
113789162 [1]

Overlapping transcripts

antisense

OTTHUMT00000256417

AC106864.1001

Intron 8

ENST0000034442

LARP7, intron 8

ENST00000324052

LARP7, HUMAN

intron 8

ENST00000308878

G4G0352, intron 8

Genome context[View flanking features](#)

< 10kb from hsa-mir-302b

Clustered miRNAs	hsa-miR-302b	4: 113789090-113789162
	hsa-miR-302c	4: 113788968-113789035
	hsa-miR-302a	4: 113788788-113788856
	hsa-miR-302d	4: 113788609-113788676
	hsa-miR-367	4: 113788479-113788546
Database links	HGNC: 31763, MIRN302B	
Gene family	MIPF00000715, miR-302	

Mature sequence MIMAT0000715

Accession	MIMAT0000715
ID	hsa-miR-302b
Sequence	47: ... sequence ... 69 Get sequence
Evidence	experimental; cloned [1-2]; Northern [1] MIRANDA: hsa-miR-302b
Predicted targets	TARGETSCAN: hsa-miR-302b PICTAR-VERT: hsa-miR-302b PICTAR-VERT: hsa-miR-302b

Minor miR* sequence MIMAT0000714

Accession	MIMAT0000714
ID	hsa-miR-302b*
Sequence	32: ... sequence ... Get sequence
Evidence	experimental; cloned [1-2]; Northern [1] MIRANDA: hsa-miR-302b
Predicted	MIRANDA: hsa-miR-302b

targets

TARGETSCAN: hsa-miR-302b

References

1

"Human embryonic stem cells express a unique set of microRNAs"
Suh MR, Lee Y, Kim JY, Kim SK, Moon SH, Lee JY, Cha KY, Chung HM,
Yoon HS, Moon SY, Kim VN, Kim KS
Dev Biol. 270:488-498(2004)

2

"A mammalian microRNA expression atlas based on small RNA library
sequencing"
Landgraf P, Rusu M, Sheridan R, Sewer A, Jovine N, Avizien A, Pfeffer S,
Rice A, Kamphorst AO, Landthaler M, Lin C, Sockan ND, Hermida L, Fulci
V, Charette S, Foa R, Schliwke J, Fuchs U, Novosek A, Muller RU,
Schermer B, Bissels U, Imman J, Phan Q, Chien M
Cell. 129:1401-1414(2007)

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Stem-loop sequence MI0000773

Accession [MI0000773](#)ID [hsa-mir-302c](#)Symbol [HGN:MIRN302C](#)Description [Homo sapiens miR-302c stem-loop](#)

Stem-loop

[Get sequence](#)[Coordinates](#)
(NCBI36)[4:113788968-113789035](#) [\[+\]](#)[Overlapping transcripts](#)[antisense](#)

[OTTHUMT00000256417](#)
[AC105864.5](#) [\[+\]](#)
[intron 8](#)
[ENST00000344442](#)
[LARP7 intron 8](#)
[ENST00000324052](#)
[LARP7 HUMAN](#)
[intron 8](#)
[ENST00000308878](#)
[Q4G0J3-2](#) [intron 8](#)

Genome
context[View flanking features](#)[< 10kb from hsa-mir-302c](#)Clustered
miRNAs[hsa-mir-302b](#)[4:113789090-113789162](#)[hsa-mir-302c](#)[4:113788968-113789035](#)[hsa-mir-302a](#)[4:113788788-113788856](#)

[illegible]

References

1	Suh MP, Lee Y, Kim JY, Kim SK, Moon SH, Lee JY, Cha KY, Chung HM, Yoon HS, Moon SY, Kim VN, Kim KS Dev Biol. 270:488-498(2004)
2	"A mammalian microRNA expression atlas based on small RNA library sequencing" Landgraf P, Rusu M, Sheridan R, Sewer A, Jovino N, Aravin A, Pfeffer S, Rice A, Kamphorst AO, Landthaler M, Lin C, Socci ND, Hermida L, Fulci V, Chiaretti S, Foa R, Schliwka J, Fuchs U, Novosel A, Müller RU, Schermer B, Bissels U, Imman J, Phan Q, Chien M Cell. 129:1401-1414(2007)

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Stem-loop sequence MI0000774

Accession MI0000774**ID** hsa-mir-302d**Symbol** HGNC:MIRN302D**Description** Homo sapiens miR-302d stem-loop**Stem-loop**[Get sequence](#)**Comments**

Human miR-302a (MI0000738), miR-302b (MI0000742), miR-302c (MI0000733), miR-302d (MI0000774) and miR-367 (MI0000725) are clustered on chromosome 4.

Coordinates
(NCBI36)

4: 113788609
113788676
Overlapping transcripts

antisense

OTTHUMT00000256417

AC106864.1-001

Intron 8

ENST00000341442

LARP7, intron 8

ENST00000324052

LARP7, HUMAN

intron 8

ENST00000308878

Q4G0J3-2, intron 8

Genome context[View flanking features](#)

< 10kb from hsa-mir-302d

hsa-mir-302b

4: 113789090-113789162

Clustered miRNAs	hsa-miR-302c	4: 113788968-113789035
	hsa-miR-302a	4: 113788788-113788856
	hsa-miR-302d	4: 113788609-113788676
	hsa-miR-367	4: 113788479-113788546
Database links	HGNC: 31765; MIRN302D	
Gene family	MIRF0000071, miR-302	

Mature sequence MIMAT0000718

Accession	MIMAT0000718
ID	hsa-miR-302d
Sequence	<p>4415 113788609-113788676</p> <p>256</p> <p>Get sequence</p>
Evidence	experimental, cloned [1-2]; Northern [4]
Predicted targets	<p>MIRANDA: hsa-miR-302d</p> <p>TARGETSCAN: hsa-miR-302d</p> <p>PICTAR-VERT: hsa-miR-302d</p>

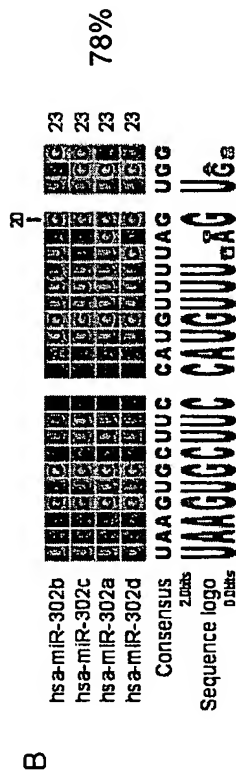
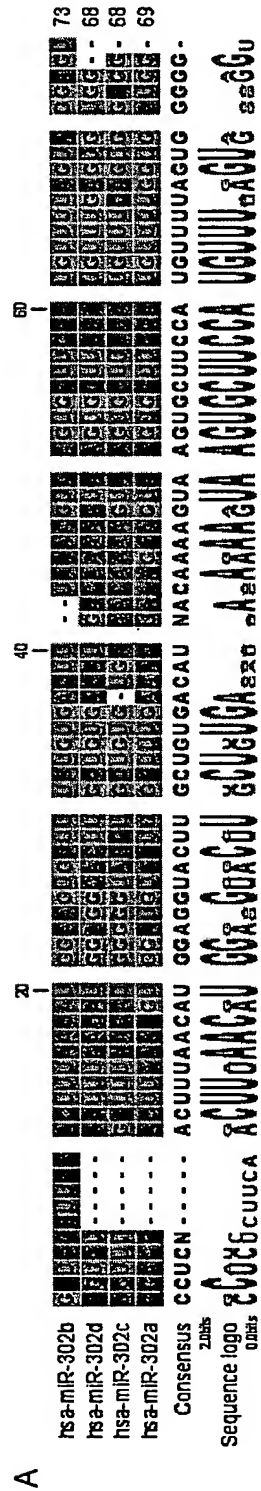
Minor miR* sequence MIMAT0004685

Accession	MIMAT0004685
ID	hsa-miR-302d*
Sequence	<p>6 22</p> <p>Get sequence</p>
Evidence	experimental, cloned [2]
Predicted targets	<p>MIRANDA: hsa-miR-302d</p> <p>TARGETSCAN: hsa-miR-302d</p>

References

- 1 "Human embryonic stem cells express a unique set of microRNAs"
Sun MR, Lee Y, Kim JY, Kim SK, Moon SH, Lee JY, Cha KY, Chung HM,
Yoon HS, Moon SY, Kim VN, Kim KS
Dev Biol. 270:488-498(2004).
- 2 "A mammalian microRNA expression atlas based on small RNA library
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Rice A, Kamphorst AO, Landthaler M, Lin C, Sockanudin H, Hermida L, Fulci
V, Chiariotti S, Foa R, Schliwka J, Fuchs U, Novosel A, Muller RU,
Schermer B, Bissels U, Imman J, Phan Q, Chien M
Cell. 129:1401-1414(2007).

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Alignment of miR-302b, miR-302c, miR-302a, and miR-302a from human genome sequence.

A. Alignment of the precursor microRNAs from human miR-302b, miR-302c, miR-302a, and miR-302d.

B. Alignment of the mature microRNAs from human miR-302b, miR-302c, miR-302a, and miR-302d.

Abbreviations: has, *Homo sapiens*;